The Polymorphisms of Uridine-diphosphoglucuronosyltransferase 1A7 and 1A10 in Taiwanese Patients with Lung Cancer

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Several carcinogens mediated cellular injury are thought to play a crucial role in the pathogenesis of lung cancer. Additionally, genetic variations that reduce the expression or activity of detoxifying enzymes such as the UDP-glucuronosyltransferases might be important in this respect. The aim of this study is to investigate the hypothesis that frequency distribution of polymorphisms in the UGT1A7 and UGT1A10 genes is associated with occurrence of lung cancer in Taiwanese population.

The method of polymerase chain reaction-restriction fragment length polymorphism was utilized to analyze nucleotides -57, 33, 387, 391, 392, and 622 of the UGT1A7 gene, and nucleotides 605, and 693 of the UGT1A10 gene in 100 lung cancer patients and 100 healthy controls. The results showed that lung cancer was inversely associated with the variation of UGT1A10 at nucleotide 693 (odds ratio [OR]: 0.276; 95% confidence interval [CI]: 0.097~0.787; p = 0.011). The nucleotide changes of UGT1A7 at position -57, 33, and 622 showed significant correlation with position 387, 391, and 392 (r = 0.52, p < 0.0001). Furthermore, we found that the risk of lung cancer had the higher level of frequency in haplotype of wild-type UGT1A10-693 / variant UGT1A7-622 (OR: 8.77; 95% CI: 1.10~70.8; p = 0.02). We did not detect any association between lung cancer and UGT1A7 polymorphisms in Taiwanese population. Nevertheless, this study demonstrated the novel findings that determination for nucleotide 693 of the UGT1A10 gene may be useful to identify individuals susceptible to lung cancer and take measures to prevent development of this disease.

Key words: Lung cancer, UDP-glucuronosyltransferases, genetic polymorphisms, synergistic effects

Introduction

The high incidence of lung cancer is a major public health problem worldwide [1]. In Taiwan, lung cancer has become the leading cause of cancer-related deaths in both men and women [2]. Studies have shown that lung cancer cases are caused by smoking, air pollution, environmental risk factors (e.g., exposures to radiation, asbestos, heavy metals, and polycyclic aromatic hydrocarbon) [3, 4]. Especially,
smoking is a well-established risk factor for lung cancer in Taiwan. Smoking contains several carcinogens, including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) or benzo-\((a)\)-pyrene and hydroxylated benzo-\((a)\)-pyrenes [5]. Although these carcinogens are established risk factors for lung cancer, genetic diversity also plays an important role in determining the ultimate outcome following exposure to carcinogens. Certain genetic polymorphisms of several genes have been associated with individual susceptibility to lung cancer due to their ability to modify the effect of carcinogens. Individual susceptibility to lung cancer has been shown to vary with the presence of single nucleotide polymorphisms (SNPs) in a variety of critical genes [6, 7]. Polymorphisms in genes involved in the metabolic activation (cytochrome P450) and detoxification (UDP-glucuronosyltransferases (UGTs)) of carcinogens as well as in the repair of DNA damage (8-oxoguanine DNA glycosylase 1) have all been associated with an increased risk of lung cancer in case–control studies [8, 9].

The human UGTs represent an enzyme superfamily that catalyze the glucuronidation of diverse compounds, including therapeutic drugs, endogenous metabolites (e.g., bilirubin and steroid hormones), and known human carcinogens (e.g., heterocyclic and polycyclic hydrocarbons and heterocyclic amines) by glucuronidation reaction. UGTs can catalyze the conjugation of hydrophobic compounds of divergent chemical classes to form water-soluble \(\beta\)-D-glucopyranosiduronic acids. These metabolites subsequently undergo renal or biliary elimination from the body [10, 11, 12]. Furthermore, UGTs have been regarded as major biochemical factors in cellular defense and detoxification.

Based on structural and sequence homology, UGTs are classified into several families and subfamilies [13]. UGT2B family is derived from independent genes locus in chromosome 4, whereas the entire UGT1A family is derived from a single gene locus in chromosome 2. The gene organisation is quite unique: exon 1, preceded by the respective promoter, is specific only for the UGT1A isoforms [14, 15]. Human UGT1A7 and UGT1A10 are expressed in oral, laryngeal, oesophageal, gastric and intestinal tissue [16]. mRNA and protein expression of UGT1A7 and UGT1A10 in the lung is still unclear. Previous studies have demonstrated that UGT1A7 and UGT1A10 were implicated in the conjugation and detoxification of metabolites of several carcinogens, including polycyclic aromatic hydrocarbons, such as benzopyrene (BaP) [17, 18]. Additionally, UGT1A7 and UGT1A10 allelic variants may alter individual susceptibility to cancer via decreased detoxification capacity. The allelic variants in UGT1A7 and UGT1A10 and its association with lung cancer were investigated in Japanese and Chinese populations [8, 19, 20]. As yet, the prevalence of UGT1A7 and UGT1A10 polymorphism for lung cancer has not yet been evaluated in Taiwanese population. The aim of this study was to analyze whether genetic polymorphisms present in UGT1A7 and UGT1A10 in Taiwanese lung-cancer patients.

### Materials and Methods

#### Study subjects and healthy controls

The study subjects (50 males and 50 females) were selected from Taiwanese adults who had undergone lung cancer therapy. Healthy controls (50 males and 50 females) were selected from Taiwanese adults who had undergone physical examination, with no evidence of lung or other cancers. The age and sex distributions are summarized in Table 1. All subjects were interviewed with a questionnaire including demographic characteristics, individual lifestyle and history of disease by professional trained interviewers. To ensure the validity of data, with the subjects’ permission, a 5 ml blood sample was collected into ethylenediaminetetraacetic acid (EDTA) tube after interview. Written informed consent was obtained from all subjects before blood sampling.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Lung cancer patients (n = 100)</th>
<th>Healthy controls (n = 100)</th>
<th>(p)-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>50/50</td>
<td>50/50</td>
<td>NS</td>
</tr>
<tr>
<td>Median age (range, yr)</td>
<td>63 (34-88)</td>
<td>61 (41-83)</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\)\(p\)-values were calculated by Student’s \(t\)-test for comparing the case and control-group parameters.
Committee.

Genomic DNA preparation in blood specimens

Total genomic DNA was purified from peripheral leukocytes using the blood DNA isolation kit (Maxim Biotech Inc., San Francisco, USA) and stored at -20°C until analysis according to the manufacturer’s instructions.

Qiagen spin column extraction in lung tissue specimens

The commercial QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) to isolate tissues DNA. The extraction procedure was performed according to the manufacturer’s instruction (QIAamp). Paraffin wax embedded tissues are a valuable source of DNA for analysis. The extraction procedure was performed according to the manufacturer’s instruction (QIAamp). Paraffin wax embedded tissues were dewaxed, tissues were digested with 200 µl of ATL buffer containing proteinase K at 200 µg/ml overnight at 56 °C. After digestion, 200 µl of AE buffer was added and incubated at 70 °C for 10 minutes, followed by mixing with 200 µl of 100% ethanol. The solution was transferred into a spin column, centrifuged at 8000 rpm for one minute, and washed with AW1 and AW2 buffers. DNA was eluted with 50 µl of AE buffer incubated at room temperature for 5 min. The extracted DNA was collected after further centrifugation.

UGT1A7 and UGT1A10 polymorphisms assay

The six known variants (-57T>G in the promoter area and nucleotides 33C>T, 387C>T, 391C>T, and 622T>C) in the UGT1A7 gene and the two known variants (nucleotides 605C>T and 693C>T) in the UGT1A10 gene, which had been determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) [21, 22] were assayed for our study subjects. The primers used for PCR are shown in Table 2. The PCR reaction mixture contained 1 µg/µl of DNA in 10 mmol/L Tris-HCl (pH 8.8), 20 mM MgCl2, 10 µM of each dNTP, 10 µM of each primer, and 5 µl of AL buffer was added and incubated at 70 °C for 10 minutes, followed by mixing with 200 µl of 100% ethanol. The solution was transferred into a spin column, centrifuged at 8000 rpm for one minute, and washed with AW1 and AW2 buffers. DNA was eluted with 50 µl of AE buffer incubated at room temperature for 5 min. The extracted DNA was collected after further centrifugation.

Table 2. Natural or mutagenesis primers, restriction enzymes, and the results for UGT1A7 and UGT1A10 variations in Taiwanese

<table>
<thead>
<tr>
<th>Position (cDNA)</th>
<th>Primer</th>
<th>Restriction enzyme</th>
<th>Result (bp)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>U7F1</td>
<td>5’TGAATGAATAAGTACACGCC3’</td>
<td>HpyCH4IV</td>
</tr>
<tr>
<td></td>
<td>U7R1</td>
<td>5’ATAGGAGAAAATGACCTTGCC3’</td>
<td>Taq I</td>
</tr>
<tr>
<td></td>
<td>U7-33F1</td>
<td>5’GGGGGCAAAATAATGTTGC3’</td>
<td>Alu</td>
</tr>
<tr>
<td></td>
<td>U7-33R</td>
<td>5’ACTGCACTGTTGAAACATCG3’</td>
<td>Rsa I</td>
</tr>
<tr>
<td></td>
<td>U7-387F</td>
<td>5’AAATGGITGCTTGA3’</td>
<td>Hpa II</td>
</tr>
<tr>
<td></td>
<td>U7-387R</td>
<td>5’GGGAAAATATCCCGC3’</td>
<td>Rsa I</td>
</tr>
<tr>
<td></td>
<td>U7-391F</td>
<td>5’GGCAAAATATTCCCCTGG3’</td>
<td>Msp I</td>
</tr>
<tr>
<td></td>
<td>U7-391R</td>
<td>5’CAGGAGTTTGTTTAATGATC3’</td>
<td>Hpa I</td>
</tr>
</tbody>
</table>

*Underscoring indicates mutagenesis site; Size of PCR product; Digestion result of wild type; Digestion result of variant
Espoo, Finland) in a final volume of 50 µl. The reaction mixtures were incubated at was performed by DNA automated thermocycler (Applied Biosystems, Gene Amp System 2400, USA) as follows: three cycles of denaturation at 94 °C for 80 s, annealing at 55 °C for 60 s, and primer extension at 72 °C for 110 s; seven cycles of denaturation at 94 °C for 60 s, annealing at 55 °C for 60 s, and extension at 72 °C for 110 s; 30 cycles of denaturation at 94 °C for 50 s, annealing at 55 °C for 50 s, and extension at 72 °C for 90 s. A final extension at 72 °C for 10 min was performed to ensure complete extension of PCR products. The PCR products were directly sequenced with an automated fluorescence sequencer (ABI Prism377, PE Applied Biosystems, Foster City, CA) according to the manufacturer’s instructions.

**Restriction fragment length polymorphism (RFLP) assay**

The RFLP analysis was performed at 37 °C for 18 h using 10-15 µl PCR product and 5 U of the appropriate restriction enzyme (HpyCH4IV for UGT1A7 promoter area -57, Taq I for UGT1A7 nucleotide 33, Afl II for UGT1A7 nucleotide 387, Hpa II for UGT1A7 nucleotide 391, Tag II for UGT1A7 nucleotide 392, Rsa I for UGT1A7 nucleotide 622, Mly I for UGT1A10 nucleotide 605, and Alu I for UGT1A10 nucleotide 693). All enzymes were purchased from New England Biolabs, Beverly, MA. The RFLPs then were confirmed by electrophoresis in 7 % polyacrylamide or 2 % agarose gels that were stained subsequently with ethidium bromide and evaluated under ultraviolet light using a computerized photoimaging system (Bio-Rad Gel Doc 2000, USA).

**Statistical analysis**

The collected data were analyzed using Statistical Package for Social Sciences software (SPSS, version 10.0; SPSS Inc., Chicago, IL). The Student’s t-test was used for comparing the case and control-group parameters. To evaluate the contribution of each genetic allele, simple and multivariate logistical regressions, as appropriate, were used for the calculation of the relevant odds ratio (OR) and the 95% confidence interval (CI) for lung cancer. P value (p <0.05) or 95% CI for the OR above or below 1.0 was defined as constituting statistical significance.

### Results

#### Characteristics of patients and controls

The basic demographic data for the lung cancer patient and healthy control groups were tabulated in Table 1. The proportion of male and female was not different between patients and controls. In addition to, there were no significant differences between the two groups in regard to mean age and distribution of age.

#### Association between UGT1A7 genetic polymorphisms and lung cancer

The prevalence of UGT1A7 (genotypes) alleles and presence of lung cancer are compared in Table 3. Univariate logistic regression was utilized to evaluate the contribution of each genotype and genetic allele. No statistical differences were observed in the distribution of the UGT1A7 (genotypes) alleles among patient and control groups as a whole. These findings indicate that individuals carrying low-activity UGT1A7 genotypes (alleles) do not run a higher risk of lung cancer in Taiwanese population.

#### Association between UGT1A10 polymorphisms and lung cancer

As shown in Table 4, there was no significant in the prevalence of the UGT1A10 nucleotide 605 polymorphic variant between case patients and healthy control. A significantly higher prevalence of the UGT1A10 nucleotide 693 polymorphic variant was observed in healthy-control than in case patients. As afore mentioned that the UGT1A10 nucleotide 693 polymorphic variant exhibited a significant decrease in risk for lung cancer (OR: 0.276; 95% CI: 0.097~0.787; p = 0.011). As expected, in lung tissues aspect, we also have found that the UGT1A10 nucleotide 693 polymorphic variant presented a significant decrease in risk of lung cancer occurrence (OR: 0.312; 95% CI: 0.117~0.827; p = 0.015) (Table 5).

#### Linkages between UGT1A10 nucleotide 693 and UGT1A7 polymorphisms and among UGT1A7 polymorphisms
The interaction of the UGT1A10 nucleotide 693 and UGT1A7 polymorphisms and that among UGT1A7 polymorphisms are shown in Table 6. The results demonstrated that UGT1A10 nucleotide 693 was not associated with UGT1A7 polymorphisms. We also found that the nucleotide change of UGT1A10 at position 693 showed negative but not significant correlation with position -57, 33, and 622. Furthermore, statistical analysis indicated that the nucleotide changes of UGT1A7 at position -57, 33, and 622 were significantly related to position 397, 391, and 392 \( (r = 0.52, p < 0.0001) \). Moreover, UGT1A7 at position 387, 391, 392 and -57, 33, 622 were in linkage.
Protective effect of variant UGT1A10 nucleotide 693 and wild-type UGT1A7 nucleotide 622 against lung cancer

The frequencies of wild-type UGT1A10-693/variant UGT1A10-622 and variant UGT1A10-693/wild-type UGT1A7-622 were compared among patient and control groups. As shown in Table 7. We found that the risk of lung cancer had the higher level of frequency in haplotype of wild-type UGT1A10-693/variant UGT1A7-622 (OR: 8.77; 95% CI: 1.10–70.0; p = 0.02). Moreover, variant UGT1A10-693 and wild-type UGT1A7-622 revealed an additive interaction effect in protecting against lung cancer in our Taiwanese population.

Discussion

In this study, we found that UGT1A10 nucleotide 605 polymorphism and three UGT1A7 variant genotypes were not involved in patients to the development of lung cancer. However, a significantly higher prevalence of the UGT1A10 nucleotide 693 polymorphic variant was observed in healthy-control than in case patients. The results of a study had demonstrated that UGT1A10 may play an important role in the detoxification of several tobacco-smoke carcinogens, such as benzo-(a)-pyrene [23, 24]. The 693 variant in the UGT1A10 genes is belonging to nonsense, and UGT1A10 nucleotide 693 variant can not alter enzymatic activity. We hypothesize that the wild type UGT1A10 at nucleotide 693 may be in linkage disequilibrium with another marker in the UGT1 locus, which may alter the function of UGT and alter individual susceptibility to lung cancer via decreased detoxifying capacity. Further studies are being carried out in our laboratory to verify these possibilities.

In previous studies have demonstrated that low-activity UGT1A7 genotypes (alleles) was associated with various cancers [11, 25, 26, 27, 28, 29]. It has been reported recently that the UGT1A7 polymorphisms evaluated in Japanese and Chinese population, the incidence of UGT1A7*3 was significantly associated with

<table>
<thead>
<tr>
<th>Table 6</th>
<th>The correlations between UGT1A7 and UGT1A10 SNP</th>
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<tbody>
<tr>
<td>UGT1A7</td>
<td>UGT1A7</td>
</tr>
<tr>
<td>-57</td>
<td>1.0</td>
</tr>
<tr>
<td>33</td>
<td>1.0</td>
</tr>
<tr>
<td>387</td>
<td>1.0</td>
</tr>
<tr>
<td>391</td>
<td>1.0</td>
</tr>
<tr>
<td>392</td>
<td>1.0</td>
</tr>
<tr>
<td>622</td>
<td>1.0</td>
</tr>
<tr>
<td>693</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Odds ratios and 95% confidence intervals for lung cancer associated with suspected gene risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene SNP</td>
<td>Number</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>UGT1A10-693</td>
<td>1/56</td>
</tr>
<tr>
<td>UGT1A10-622</td>
<td>12/56</td>
</tr>
<tr>
<td>UGT1A10-693/UGT1A7-622*</td>
<td>55/56</td>
</tr>
</tbody>
</table>

*If gene types of UGT1A10-693 are wild types or gene types of UGT1A7-622 are mutants then the risk is considered as 1, else is equal to 0.
the presence of lung cancer [8, 19]. To evaluate whether these UGT1A7 genotypes (alleles) were related to lung cancer, we calculated the genotype (allele) frequencies in the present and absence of lung cancer and found no statistically significant relationship between the two groups. The contrary results may be due to ethnic differences, limited sample size, inherent defect of case-control study or statistical power to find difference. Furthermore, the results also have demonstrated that UGT1A7 polymorphisms was not associated with UGT1A10 nucleotide 693. It has been reported that the UGT1A10 polymorphisms evaluated in Asia populations, the frequencies of each SNPs were similar [30]. There is a study indicated that incidence of oral cancer was significantly associated with the presence of UGT1A10 SNPs [31].

In this study, for the 100 patients, the results of simple logistical regressions indicated that the OR of the risk for lung cancer was 8.77 (p=0.02) for the individuals possessing UGT1A10 nucleotide 693 and variant-622 UGT1A7 allele. Therefore, the novel finding in our study was that the variation of the UGT1A7 gene was considered to constitute one of the risk factor for causing lung cancer. It was interesting to find that the variation at nucleotide 622 of the UGT1A7 gene, the most common variant of the UGT1A7 gene among our population, as well as the presence of the UGT1A10 nucleotide 693 plus variant-622 UGT1A7 allele, was demonstrated to represent a risk factor for lung cancer in Taiwan. Thereby, the result indicated that the UGT1A10 nucleotide 693 polymorphism, which may alter enzymatic activity and increase glucuronidation function for some carcinogens, to play detoxification activity of UGT1A10 and perform a protective effect.

To conclude, the present study has demonstrated the novel findings that a significantly decreased occurrence of lung cancer was related to the UGT1A10 nucleotide 693 polymorphism in Taiwan. According to this observation, determination of UGT1A10 nucleotide 693 polymorphism may provide useful information about preventive measures against lung cancer. Hence, further studies should be carried out to clarify the association between these findings and lung cancer in a larger population.

Acknowledgements

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UGT1A7 and UGTA10 polymorphisms in lung cancer


台灣肺癌患者之尿甘雙磷酸葡萄糖醛酸基轉移酶第 7/10 同功酶
基因多型性研究

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尿甘雙磷酸葡萄糖醛酸基轉移酶(UGT)可將致癌性化合物進行葡萄糖醛酸化以增加其水溶性並加速排出體外。尿甘雙磷酸葡萄糖醛酸基轉移酶之基因多型性會造成酵素的產量或代謝活性變化, 影響酵素的解毒效率並進而影響癌症的發生率。本研究將以PCR-RFLP與基因定序的方式, 偵測台灣已知具有高度流行率的3種UGT1A7基因多型性, 以及2個在黃種人身上具有高流行率的UGT1A10 SNP在台灣肺癌患者與健康人之間的流行率, 並預期這兩個代謝重要致癌物質Benzo(a)pyrene(BaP)的Phase II代謝酵素可能會是重要的肺癌易感基因。研究結果顯示, 正常人對зи照組於UGT1A10 codon 693多型性(C被T取代)的出現頻率高於肺癌病人, 在血液檢體的部分, 具有UGT1A10 codon 693 T者, 罹患肺癌的危險比(odds ratio, OR)是野生型的0.276倍(95%信賴區間, 95%C.I=0.097~0.787, p=0.011); 在組織檢體的部份, 結果仍發現非肺癌病患的UGT1A10 codon 693多型性(C被T取代)也高於肺癌病患, 且達顯著差異(危險比=0.312, 95%信賴區間=0.117~0.827, p=0.015)。此外在UGT1A7 -57、33、622與387、391、392是有顯著之變異一致相關性(r=0.52, p=0.0001)。而病患基因型若屬於UGT1A10 693野生型與UGT1A7 622多型性(T被C取代)者較UGT1A10 693多型性(C被T取代)且UGT1A7 622野生型之病患罹患肺癌之危險比高達8.77倍(95%信賴區間為1.10~0.070.0, p=0.02), 顯示這兩個基因對於肺癌之發生具有協同作用。本研究結果顯示UGT1A10 codon 693對肺癌發生具保護效果之現象, 可能原因與其他UGT基因型具有協同作用下之結果, 本研究結果可提供UGT基因為肺癌基因感受性研究之部分證據。

關鍵詞: 肺癌、尿甘雙磷酸葡萄糖醛酸基轉移酶、基因多型性、協同作用

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